TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER: SYL 550

U S APPLICATION NO. (If known, see 37 CFR 1.5): 10/030752

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/FR00/01246	09 May 2000	11 May 1999

TITLE OF INVENTION: USE OF SUCCINIC ACID DERIVATIVES TO OBTAIN A MEDICINE FOR TREATING INFLAMMATION

APPLICANT(S) FOR DO/EO/US: CAILLE, Dominique

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND or SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1)).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☒ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ An English language translation of the International Application.
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☒ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371 (c)(3)).
9. ☒ An unexecuted oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☐ An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern document(s) or information included:

11. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.

12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.

13. ☐ A FIRST preliminary amendment.

    ☐ A SECOND or SUBSEQUENT preliminary amendment.

14. ☐ A substitute specification.

15. ☐ A change of power of attorney and/or address letter.

16. ☒ Other items or information:
    Citation of References
    Information Disclosure Statement by Applicant (Form PTO-1449)

U.S. APPLICATION NO. (if known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
10/030752	PCT/FR00/01246	SYL 550

17. ☒ The following fees are submitted:

BASIC NATIONAL FEE (37 CFR 1. 492 (a)(1)-(5)):

Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and international Search Report not prepared by the EPO or JPO.....$1040.00
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO.....$890.00
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO...$740.00
International preliminary examination fee (37 CFR 1.482)paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4).....$710.00
International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfy provisions of PCT Article 33(1)-(4).....$100.000

	CALCULATIONS PTO USE ONLY	
ENTER APPROPRIATE BASIC FEE AMOUNT =	**$ 890.00**	
Surcharge of **$130.00** for furnishing the oath or declaration later than [ ]20 [ ]30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	12 -20 =	0	x $18.00	$	
Independent claims	1 - 3 =	0	x $84.00	$	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ $280.00	**$ 280.00**	
			TOTAL OF ABOVE CALCULATIONS =	**$ 1170.00**	
Reduction of 1/2 for filing by small entity, if applicable. Verified Small Entity Statement must also be filed (Note 37 CFR 1.9, 1.27, 1.28).				$	
			SUBTOTAL =	**$ 1171.00**	
Processing fee of **$130.00** for furnishing the English translation later than [ ]20 [ ]30 months from the earliest claimed priority date (37 CFR 1.492 (f)). +				$	
			TOTAL NATIONAL FEE =	**$ 1170.00**	
Fee for recording the enclosed assignment (37 CFR 1.21(h). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +				$	
			TOTAL FEES ENCLOSED =	**$ 1170.00**	
			Amount to be refunded:	$	
			Charged	**$1170.00**	

a. ☐ A check in the amount of $_____ to cover the above fees is enclosed.

b. ☒ Please charge my Deposit Account No. **19-0091** in the amount of **$1170.00** to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. **19-0091**. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

Patent Department
Sanofi-Synthelabo Inc.
9 Great Valley Parkway
P.O. Box 3026
Malvern, PA 19355
Facsimile: (610) 889-8799

Applica[illegible]
27546
PATENT TRADEMARK OFFICE

Michael D. Alexander November 7, 2001
SIGNATURE DATE

Michael D. Alexander
NAME

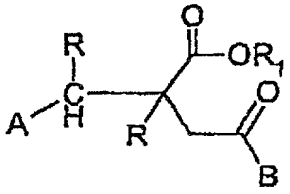
36,080
REGISTRATION NUMBER

(610) 889-8802
TELEPHONE NUMBER

USE OF SUCCINIC ACID DERIVATIVES IN PRODUCING A MEDICAMENT INTENDED FOR THE TREATMENT OF INFLAMMATION

A subject-matter of the present invention is the use of succinic acid derivatives, disclosed in Patent EP 0 507 534, in the preparation of a medicament intended for the treatment of inflammation.

Thus, a subject-matter of the present application is the use of succinic acid derivatives corresponding to the general formula (I):



(I)

in which:

A represents a phenyl group optionally substituted by one, two or three substituents chosen from a halogen or a C_{1-6} alkyl or C_{1-6} alkoxy group; a thienyl, furyl or pyridyl or a cycloalkyl having from 3 to 8 carbon atoms;

B represents [lacuna] aminobicyclic group which consists of a 5- or 6-membered cyclic amino compound condensed with a 5- or 6-membered cycloalkyl ring which can have one or two unsaturated bonds, with the condition that B is bonded to the carbon atom of the

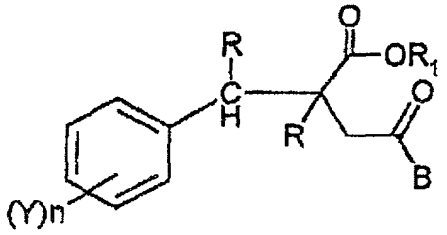
carbonyl group on the nitrogen atom; each R represents a hydrogen atom or the R residues are combined together to form a chemical bond; R_1 represents a hydrogen atom, a C_{1-6} alkyl group or an aralkyl group having from 7 to 10 carbon atoms; when there are geometrical isomers, each geometrical isomer, its E isomers and its Z isomers, its cis isomers and its trans isomers.

The compounds of general formula (I) can comprise one or more asymmetric carbon atoms. They can thus exist in the form of enantiomers or of diastereoisomers. The use of these enantiomers or diastereoisomers, and their mixtures, including racemic mixtures, forms part of the invention.

The compounds of general formula (I) can be provided in the form of the free base or of addition salts with pharmaceutically acceptable acids, as disclosed in EP 0 507 534. The use of these salts forms an integral part of the present invention.

In the present application, halogen represents an iodine, chlorine, bromine or fluorine atom.

More particularly, the use of succinic acid derivatives as defined below of formula (I):



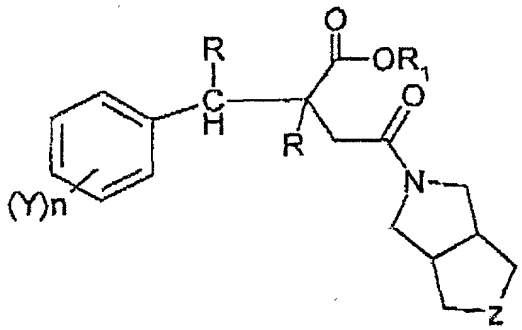
(I)

in which:

B represents [lacuna] aminobicyclic group which consists of a 5- or 6-membered cyclic amino compound condensed with a 5- or 6-membered cycloalkyl ring which can have one or two unsaturated bonds, with the condition that B is bonded to the carbon atom of the carbonyl group on the nitrogen atom; each R represents a hydrogen atom or the R residues are combined together to form a chemical bond; R_1 represents a hydrogen atom, a C_{1-6} alkyl group or an aralkyl group having from 7 to 10 carbon atoms;

Y represents a hydrogen atom, a halogen or a C_{1-6} alkyl or C_{1-6} alkoxy group and n represents 1, 2 or 3; is preferred.

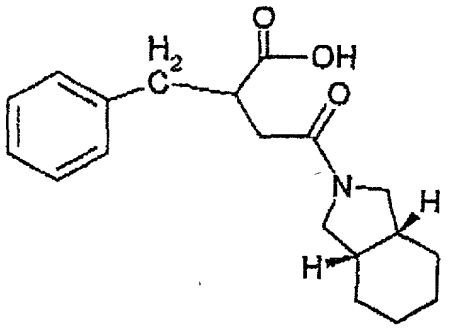
Among the latter, the preferred compounds are of formula (I):



(I)

in which Z represents an ethylene group or a vinylene group.

More specifically, the use of 2-benzyl-3-(cis-hexahydro-2-isoindolinylcarbonyl)propionic acid of formula



(I)

and more particularly of (S)-2-benzyl-3-(cis-hexahydro-2-isoindolinylcarbonyl)propionic acid is preferred.

The compounds of the invention have been subjected to biological tests intended to demonstrate their anti-inflammatory activity.

The *in vivo* activity of the compounds of the present invention were studied in an experimental model of plantar inflammation in rats.

Inflammatory oedema of the paw of rats induced by the intradermal injection of carrageenan (CAR) (1% v/v) is produced and evaluated according to the method of Winter C.A. and Risley E.A. (Carrageenan-induced edema in the hindpaw of rats as an assay for anti-inflammatory drugs. Proc. Soc. Axp. Biol. Med., 19632, 11, 544-547).

The compounds of the invention are given orally 1 hour before the injection of CAR. A 1% solution of CAR in a saline solution is injected by the s.c. route into the subplantar part of the right hind paw of rats.

The volume resulting from the inflammatory

reaction is measured by plethysmography after 1.5, 3 and 4.5 hours from the injection of CAR.

The compounds of the invention at doses of between 0.5 and 10 mg/kg by the oral route confer lasting inhibition of the inflammation induced (between 1.5, 3 and 4.5 hours after the injection of CAR) of the order of 20 to 90% with respect to the control. Preferably, the compounds of the invention exhibit at doses of 10 mg/kg inhibition of the inflammation of the order of 50 to 90%.

The results show that the compounds of the invention exhibit anti-inflammatory properties *in vivo*. They can thus be used in the symptomatic treatment of painful conditions of light to moderate intensity and/or feverish states, more particularly in diabetic neuropathies, polyarthritis, arthrosis, lumbago, traumatological pain and inflammation in the ENT field.

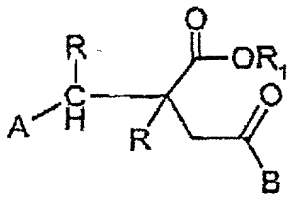
The compounds of the invention can be presented, in combination with any appropriate excipient, in any form suitable for administration via the oral or parenteral route, for example in the form of tablets, gelatin capsules, sugar-coated tablets or oral or injectable solutions, as defined in EP 0 507 534.

The compounds of the invention can be administered at daily doses of between approximately 1 and 100 mg in adults by the oral route or between

approximately 0.1 and 100 mg by the parentéral route.

Claims

1. Use of a compound of formula (I)



(I)

in which:

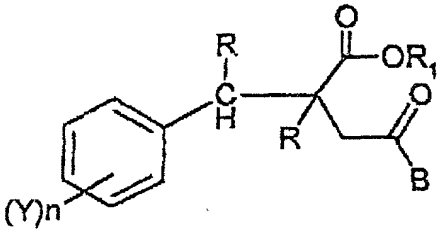
A represents a phenyl group optionally substituted by one, two or three substituents chosen from a halogen or a C_{1-6} alkyl or C_{1-6} alkoxy group; a thienyl, furyl or pyridyl or a cycloalkyl having from 3 to 8 carbon atoms;

B represents [lacuna] aminobicyclic group which consists of a 5- or 6-membered cyclic amino compound condensed with a 5- or 6-membered cycloalkyl ring which can have one or two unsaturated bonds, with the condition that B is bonded to the carbon atom of the carbonyl group on the nitrogen atom; each R represents a hydrogen atom or the R residues are combined together to form a chemical bond; R_1 represents a hydrogen atom, a C_{1-6} alkyl group or an aralkyl group having from 7 to 10 carbon atoms; when there are geometrical isomers, each geometrical isomer, its E isomers and its Z isomers, its cis isomers and its trans isomers; optionally in the form of an enantiomer or diastereoisomer or of a mixture of these various forms,

including of a racemic mixture, and the addition salts with pharmaceutically acceptable acids of one of these forms,

in the manufacture of a medicament intended for the treatment of inflammation.

2. Use according to Claim 1, characterized in that the compound of formula (I) is the compound:



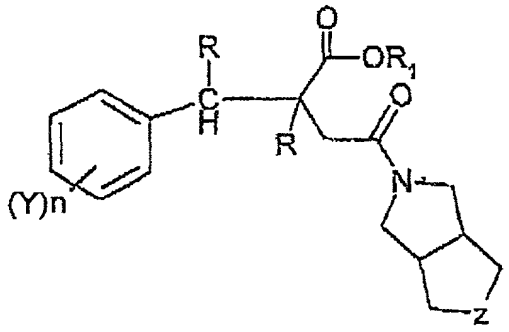
(I)

in which:

B represents [lacuna] aminobicyclic group which consists of a 5- or 6-membered cyclic amino compound condensed with a 5- or 6-membered cycloalkyl ring which can have one or two unsaturated bonds, with the condition that B is bonded to the carbon atom of the carbonyl group on the nitrogen atom; each R represents a hydrogen atom or the R residues are combined together to form a chemical bond; R_1 represents a hydrogen atom, a C_{1-6} alkyl group or an aralkyl group having from 7 to 10 carbon atoms;

Y represents a hydrogen atom, a halogen or a C_{1-6} alkyl or C_{1-6} alkoxy group and n represents 1, 2 or 3.

3. Use according to Claim 1, characterized in that the compound of formula (I) is the compound



(I)

in which Z represents an ethylene group or a vinylene group.

4. Use according to Claim 1, characterized in that the compound is (S)-2-benzyl-3-(cis-hexahydro-2-isoindolinylcarbonyl)propionic acid.

5. Use according to any one of Claims 1 to 4, characterized in that the medicament is intended for the symptomatic treatment of painful conditions of light to moderate intensity and/or feverish states.

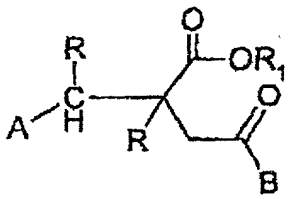
6. Use according to any one of Claims 1 to 4, characterized in that the medicament is intended for the treatment [lacuna] diabetic neuropathies, polyarthritis, arthrosis, lumbago, traumatological pain and inflammation in the ENT field.

USE OF SUCCINIC ACID DERIVATIVES IN PRODUCING A MEDICAMENT INTENDED FOR THE TREATMENT OF INFLAMMATION

SANOFI-SYNTHELABO

Abstract:

A subject-matter of the present invention is the use of succinic acid derivatives of general formula (I):



(I)

in which:

A represents a phenyl group optionally substituted by one, two or three substituents chosen from a halogen or a C_{1-6} alkyl or C_{1-6} alkoxy group; a thienyl, furyl or pyridyl or a cycloalkyl having from 3 to 8 carbon atoms;

B represents [lacuna] aminobicyclic group which consists of a 5- or 6-membered cyclic amino compound condensed with a 5- or 6-membered cycloalkyl ring which can have one or two unsaturated bonds, with the condition that B is bonded to the carbon atom of the carbonyl group on the nitrogen atom; each R represents

a hydrogen atom or the R residues are combined together to form a chemical bond; R_1 represents a hydrogen atom, a C_{1-6} alkyl group or an aralkyl group having from 7 to 10 carbon atoms; when there are geometrical isomers, each geometrical isomer, its E isomers and its Z isomers, its cis isomers and its trans isomers, in the treatment of inflammation.

Attorney Docket No.SYL550/DK

DECLARATION AND POWER OF ATTORNEY FOR UNITED STATES PATENT APPLICATION

__X__ Original _____ Supplemental _____ Substitute

As a below-named inventor, I hereby declare that:

My residence, citizenship and mailing address are given below under my name.

I/We believe that I/we am/are the original and first inventor(s) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

USE OF SUCCINIC ACID DERIVATIVES TO OBTAIN A MEDICINE FOR TREATING INFLAMMATION

the application for which

____ is attached hereto.

___	was filed on	_____	as United States
	Application Serial No.	_____	
	and was amended on	_____	(if applicable)
X	was filed on	9 May 2000	as PCT International
	Application No.	PCT/FR00/001246	
	and was amended on	_____	(if applicable)

I/We have reviewed and understand the contents of the above-identified application, including the claims, as amended by any amendment specifically referred to above.

I/We acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me/us to be material to patentability as defined in Section 1.56 of Title 37 of the Code of Federal Regulations, including for continuation-in-part applications, material information which became available between the filing date of the prior application and the national or PCT international filing date of the continuation-in-part application.

I/We hereby claim foreign priority benefit under Section 119 (a) - (d) of Title 35 of the United States Code of any foreign application(s) for patent or inventor's certificate or of any PCT international application(s) designating at least one country other than the United States identified below and also identify below any foreign application(s) for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States filed by me on the same subject matter and having a filing date before that of the application(s) from which priority is claimed:

			Priority Claimed	
Country	Number	Filing Date	Yes	No
FR	99/05978	11 May 1999	X	

I/We hereby claim benefit under Section 119(e) of Title 35 of the United States Code of any United States provisional application(s) identified below:

Application No.	Filing Date

I/We hereby claim benefit under Section 120 of Title 35 of the United States Code of any United States application(s) or PCT international application(s) designating the United States identified below:

Application Serial No.	Filing Date	Status

I/We hereby appoint Michael D. Alexander, Reg. No. 36,080; and Paul E. Dupont, Reg. No. 27,438, or any of them my/our attorneys or agents with full power of substitution and revocation to prosecute this application and to transact all business in the United States Patent and Trademark Office connected therewith.

SEND CORRESPONDENCE TO:

Patent Department
Sanofi-Synthelabo Inc.
9 Great Valley Parkway
P.O. Box 3026
Malvern, PA 19355

DIRECT TELEPHONE CALLS TO:

MICHAEL D. ALEXANDER

Telephone No. 610-889-8802

I/We hereby declare that all statements made herein and in the above-identified application of my/our own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full name of sole inventor Dominique CAILLE

Inventor's signature _____ Date _____

Mailing Address/Residence 14, sentier des Essarts, F-92190 Meudon, France

Citizenship France

Attorney Docket No.

I/We hereby claim benefit under Section 119(e) of Title 35 of the United States Code of any United States provisional application(s) identified below:

Application No.	Filing Date

I/We hereby claim benefit under Section 120 of Title 35 of the United States Code of any United States application(s) or PCT international application(s) designating the United States identified below:

Application Serial No.	Filing Date	Status

I/We hereby appoint Michael D. Alexander, Reg. No. ~~36,080~~; and Paul E. Dupont, Reg. No. 27,438, or any of them my/our attorneys or agents with full power of substitution and revocation to prosecute this application and to transact all business in the United States Patent and Trademark Office connected therewith.

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Patent Department
Sanofi-Synthelabo Inc.
9 Great Valley Parkway
P.O. Box 3026
Malvern, PA 19355

DIRECT TELEPHONE CALLS TO:

Telephone No.

I/We hereby declare that all statements made herein and in the above-identified application of my/our own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full name of first inventor CAILLE Dominique

Inventor's signature Caille Date 6-12-01

Mailing Address/Residence 14 sentier des Essarts; FR-92190 MEUDON, France FRX

Citizenship